NATIONAL GUIDELINE CLEARINGHOUSE™ (NGC™) GUIDELINE SYNTHESIS

MANAGEMENT OF EARLY STAGE BREAST CANCER

Guidelines

1. *Institute for Clinical Systems Improvement (ICSI). Breast cancer treatment. Bloomington (MN): Institute for Clinical Systems Improvement; 2000 Jan. 36 p. [56 references]
   CURRENT NGC SUMMARY: Breast cancer treatment. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2001 Aug. 38 p. [53 references].
2. Scottish Intercollegiate Guidelines Network (SIGN). Scottish Cancer Therapy Network. Breast cancer in women. Edinburgh (UK): SIGN, 1998 Oct. 62 p. [216 references]
3. American College of Radiology.
   - *Standards for diagnosis and management of ductal carcinoma in situ (DCIS) of the breast. CA Cancer J Clin 1998 Mar-Apr;48(2):108-28 [53 references]
     CURRENT NGC SUMMARY: Standards for the management of ductal carcinoma in situ of the breast (DCIS). CA Cancer J Clin 2002 Sep-Oct;52(5):256-76 [104 references].
   - *Standards for diagnosis and management of invasive breast cancer. CA Cancer J Clin 1998 Mar-Apr;48(2):83-107 [46 references]
     CURRENT NGC SUMMARY: Standards for breast conservation therapy in the management of invasive breast carcinoma. CA Cancer J Clin 2002 Sep-Oct;52(5):277-300 [82 references].
4. Cancer Care Ontario Practice Guidelines Initiative (CCOPGI). Toronto, Ont. Canada.
   - *Management of ductal carcinoma in situ of the breast. 1998 Jan 20 (updated online 2000 Jul). Cancer Prev Control 1998;2(6):312-9 [20 references; 31 references (update)].
     CURRENT NGC SUMMARY: Management of ductal carcinoma in situ of the breast. Toronto (ON): CCOPGI; 2002 Feb [online update]. Various p. (Practice guideline report; no. 1-10). [20 references].
   - *Surgical management of early stage invasive breast cancer (stage I and II). 1996 Feb 14 (updated online 2000 Jul). Cancer Prev Control 1997;1(1):10-7 [20 references].
     CURRENT NGC SUMMARY: Surgical management of early stage invasive breast cancer (stage I and II). Toronto (ON): CCOPGI; 2002 Jan [online update]. Various p. (Practice guideline report; no. 1-1). [20 references].
   - *Breast irradiation in women with early stage invasive breast cancer following breast conservation surgery. 1997 Mar 11. (updated online 2000 Jul) Cancer Prev Control Aug 1997;1(3):228-40 [12 references]. CURRENT NGC SUMMARY:

Breast irradiation in women with early stage invasive breast cancer following breast conservation surgery. Toronto (ON): CCOPGI; 2002 Jan [online update]. Various p. (Practice guideline report; no. 1-2). [61 references]

- *Adjuvant systemic therapy for node-negative breast cancer. 1998 Nov 12 (updated online 2000 Jul). Curr Oncol 1999;6(2):78-89 [50 references]. CURRENT NGC SUMMARY: Adjuvant systemic therapy for node-negative breast cancer. Toronto (ON): Cancer Care Ontario (CCO); 2002 Feb. Various p. (Practice guideline; no. 1-8). [50 references]

***Please note:** Institute for Clinical Systems Improvement (ICSI) has updated its guideline, American College of Radiology (ACR) has updated both guidelines and Cancer Care Ontario Practice Guidelines Initiative (CCOPGI) has updated four guidelines. The National Guideline Clearinghouse is working to update this synthesis and will post the update as soon as possible.

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INTRODUCTION:

Guidelines issued by ICSI, SIGN, ACR/ACS/CAP/SSO and CCOPGI for the treatment of early-stage breast cancer are compared in the following tables. For the purpose of this synthesis, early- stage breast cancer includes ductal carcinoma in situ (DCIS; Stage 0) and Stages I and II breast carcinoma.

Table 1 compares the scope and content of the guidelines. Recommendations for the management of early stage breast cancer are compared in Table 2, while Table 3 compares the benefits and harms of treatment. The comparisons in Tables 2 and 3 are restricted to aspects of initial treatment, including surgical management, radiation therapy, and adjuvant therapy. Therefore, treatment of recurrences as well as therapies directed to possible sequelae of the initial therapy (e.g., lymphedema) are excluded. Likewise, treatment recommendations pertaining to more advanced (i.e., Stage III or metastatic) disease are excluded. Finally, recommendations pertaining to diagnosis are not included.

Following the content comparison table and discussion, the areas of agreement and differences among the guidelines are identified. In general, the timing of the guideline with respect to available data is an important factor to consider when evaluating areas of differences among these guidelines. The rationale behind disparate recommendations that are not attributable to the available evidence base is also explored in the discussion of the areas of differences.

ICSI and SIGN characterized the evidence supporting the major recommendations; the definitions of the rating schemes are included in Table 4.

Abbreviations used in the text and tables follow:

- AC, doxorubicin/cyclophosphamide
- ACR/ACS/CAP/SSO, American College of Radiology, American College of Surgeons, College of American Pathologists, Society of Surgical Oncology
- CCOPGI, Cancer Care Ontario Practice Guidelines Initiative
- CMF, cyclophosphamide, methotrexate,5- fluorouracil
- DCIS, ductal carcinoma in situ
- EIC, extensive intraductal component
- ER, estrogen (oestrogen) receptor
- FNA, fine needle aspirate (aspiration)
- FNAC, fine needle aspirate cytology
- ICSI, Institute for Clinical Systems Improvement
- PR, progesterone receptor
- SIGN, Scottish Intercollegiate Guidelines Network
- XRT, radiation therapy

TABLE 1: COMPARISON OF SCOPE AND CONTENT	
	Objective and Scope
ICSI (2000)	• To improve access to all appropriate options for primary therapy for patie early breast cancer. • To standardize application of appropriate treatment modalities (surgery, r and systemic therapy) and follow-up schedules. • To increase the use of standardized education materials and psychosocia support for patients and families.

	• To enhance awareness of the importance of clinical trials.
SIGN (1998)	• To provide evidence-based recommendations about best clinical practice cancer centers, cancer units and primary care to produce their own local guidelines for the management of patients with breast cancer.
ACR/ACS/CAP/SSO (1998)	DCIS • To guide physicians in the diagnosis and management of DCIS of the bre Stage I and II • To provide standards for diagnosis and management of invasive breast carcinoma.
CCOPGI (1996-2000)	DCIS • To make recommendations about the management of DCIS of the breast Surgical management/Stage I and II • To make recommendations about surgical management and techniques i treatment of early stage invasive breast disease (Stage I and II). Breast irradiation • To make recommendations regarding the use of breast irradiation in wom early stage invasive breast cancer following breast conservation surgery. Adjuvant therapy • To make recommendations regarding the use of adjuvant systemic therap node-negative breast cancer.
	Target Population
ICSI (2000)	All patients with the diagnosis of breast cancer (ductal carcinoma in situ, early sta II] invasive breast carcinoma) who are candidates for treatment.
SIGN (1998)	Women with early operable breast cancer (TNM Stages T1-2, N0-1).
ACR/ACS/CAP/SSO (1998)	DCIS

	• Patients with ductal carcinoma in situ of the breast. Stage I and II • Women with early breast cancer (Stage I and II).
CCOPGI (1996-2000)	DCIS • Adult patients with ductal carcinoma in situ of the breast. Surgical management/Stage I and II • Women with early stage invasive breast cancer (Stage I and II). Breast irradiation • Women with early stage (Stages I and II) breast cancer who have underg breast conserving surgery. Adjuvant therapy • Women with node-negative breast cancer [Stages 0–I, and some women Stages II-III].
	Interventions and Practices
ICSI (2000)	*Evaluation* 1. Bilateral mammogram 2. Biopsy *Treatment* 1. Patient education 2. Lumpectomy and radiation therapy (breast conservation treatment) 3. Mastectomy and radiation therapy 4. Mastectomy, reconstruction, and radiation therapy 5. Axillary dissection 6. Adjuvant chemotherapy 7. Follow-up (annual mammograms, clinical breast examination, chest x-ray chemistries, bone scans, and soluble tumor markers)
SIGN (1998)	1. Breast screening for women under 50 yrs, 50-64 yrs and 65 yrs and older 2. Breast self-examination 3. Symptoms and referral, including conditions that can be initially managed

	general practice and those that require referral to a breast specialist 4. Imaging 5. Surgery (breast conservation: mastectomy, reconstruction, axilla surgery) 6. Adjuvant radiotherapy 7. Adjuvant systemic therapy (chemotherapy; hormonal therapy) 8. Psychosocial treatment 9. Follow up strategies for patient and local general practitioner 10. Nursing care
ACR/ACS/CAP/SSO (1998)	**DCIS:** *Evaluation* 1. History and physical examination 2. Mammographic evaluation 3. Surgical biopsy 4. Pathologic evaluation *Treatment Options* 1. Mastectomy 2. Breast-conserving surgery (lumpectomy) and radiation therapy 3. Breast-conserving surgery alone 4. Role of tamoxifen **Stage I and II:** *Evaluation* 1. History and physical examination 2. Mammographic evaluation 3. Pathologic evaluation 4. Patient preferences *Treatment* 1. Breast conservation surgery 2. Radiation therapy Follow-up history, physical examination and mammography
CCOPGI (1996-2000)	**DCIS:** 1. Breast conserving surgery (lumpectomy) 2. Total mastectomy 3. Total mastectomy with reconstruction 4. Radiation therapy 5. Role of tamoxifen **Surgical management/Stage I and II:** 1. Breast conservation therapy (lumpectomy with axillary dissection; radioth

	and further surgery, if necessary) 2. Modified radical mastectomy **Postoperative breast irradiation in women with early stage invasive brea cancer, by the following fractionation schedules:** 1. 50 Gy in 25 fractions to the whole breast 2. 40 Gy in 16 fractions to the whole breast with a local boost to the primary 12.5 Gy in five fractions 3. 54 Gy in 27 fractions to the whole breast 4. 50 Gy in 25 fractions to the whole breast plus a boost to the tumor bed of 5 fractions **Adjuvant systemic therapy:** 1. Tamoxifen: oral tamoxifen 20 mg daily for five years 2. Chemotherapy regimen: polychemotherapy should reasonably be compri six cycles of CMF or four cycles of AC

TABLE 2: COMPARISON OF RECOMMENDATIONS FOR THE MANAGEMENT OF EARLY BREAST C

	Treatment Options: Discussion with Patient
ICSI (2000)	All potential options are reviewed with the patient and her significant other(s) whe appropriate. It is important to include all possible treatment options (based on the results) at this visit. Breast conservation vs. mastectomy needs to be discussed ir the rationale for the selection of the type of procedure. The anticipated cosmetic appearance should be discussed with the patient prior to choosing a surgical opti Reconstruction should be offered to women with Stage 0-II breast cancer who rec desire mastectomy. Consideration needs to be given to the resources that may be needed based c type of surgery and/or degree of involvement. It is important to assist the patie her significant other(s) to have a seamless system of care. The following is a suggestion of services that the practitioner should consider: • Radiation therapy • Patient education • General surgery • Medical oncology • Plastic surgery (Evidence supporting this conclusion is of class: R)
SIGN (1998)	Prior to performing any definitive treatment, the patient should be fully discussed multidisciplinary team. (Recommendation grade C) Patients should be fully informed of the different options of treatment. (Recommendation grade C)

	Patients should be staged using the TNM classification system. (Recommenda grade C) All patients with T1-3, N0-1, M0 should be considered for primary surgery. Sor patients with larger T2 (>3cm) or T3, N0 or 1, M0 may be considered for prima systemic therapy (neoadjuvant) prior to surgery. Elderly fit patients (≥70 years) potentially operable tumors should be managed in the same way as younger v rather than giving tamoxifen as sole therapy. (Recommendation grade A) There are three established surgical procedures for invasive breast cancers: (local excision, (2) quadrantectomy or segmentectomy and (3) mastectomy. Bo and (2) would normally be followed by radiotherapy. The combination of wide l excision or segmentectomy and radiotherapy is often called breast conservatio Randomized controlled clinical trials have shown that in tumors up to 4 cm in s treatment by mastectomy or breast conservation produces identical overall su Many women are distressed at the prospect of a mastectomy. For these wome discussion of some form of breast reconstruction may help.
ACR/ACS/CAP/SSO (1998)	**DCIS, and Stage I and II.** Perhaps the most difficult aspect of patient evaluation i assessment of the patient's needs and expectations regarding breast preservatio patient and her physician must discuss the benefits and risks of mastectomy com with breast-conservation treatment in her individual case, with thoughtful consider each. Each woman must evaluate how her choice of treatment is likely to affect her s disease control, self-esteem, sexuality, physical functioning, and overall quality Several factors should be considered, including (1) long-term survival; (2) the possibility and consequences of local recurrence; and (3) psychological adjust (including the fear of cancer recurrence), cosmetic outcome, sexual adaptatio functional competence. *Selection of treatment in DCIS* Without mature data from clinical trials, it is the collective responsibility of the s pathologist, radiation oncologist, and radiologist to integrate all available data treatment options and recommendations can be articulated clearly to the patie The surgeon must decide, based on imaging studies and the pathology consu report, whether the patient is a candidate for a breast-conserving approach. If recurrence must be further discussed. Local recurrence with total mastectomy Local recurrence is observed at a higher rate in patients treated with breast conservation, but the impact of these local recurrences on overall survival is p small. Finally, patients need to understand the excellent prognosis for this dise either surgical approach. *Patient selection and evaluation for treatment of early-stage breast cancer* Because of the potential options for treatment of early-stage breast cancer, ca patient selection and a multidisciplinary approach are necessary.
CCOPGI (1996-2000)	**DCIS.** Women with ductal carcinoma in situ of the breast who are candidates for l conserving surgery should be offered the choice of lumpectomy or total mastecto

	Mastectomy with the option for reconstruction remains an acceptable choice for w preferring to maximize local control. **Stage I and II.** Women with early stage invasive breast cancer (Stage I and II) candidates for breast conservation therapy should be offered the choice of eitl breast conservation therapy (excision of tumor with clear margins and axillary dissection) or modified radical mastectomy. The choice is an individual one for patient and thus she should be fully informed of the options including the risks benefits of each procedure. She should be informed that breast irradiation is p procedure for breast conservation therapy. In addition, she should be aware o potential need for further surgery if the margins are positive.
	Conservation Surgery Eligibility
ICSI (2000)	Breast conservation therapy is defined as excision of the primary tumor and adjac breast tissue, followed by XRT of the whole breast or the breast and regional lym nodes. Exclusion criteria for conservation management (outside of clinical trials) are: • Diffuse microcalcifications • Gross multicentric disease or gross multifocal disease • Lesions >5 cm • Inflammatory carcinoma • Previous significant radiation treatment which included breast in the field Relative contraindications include pregnancy and collagen vascular disease in lupus and scleroderma. Note that exclusion based on age, central lesions, or h subtype is not appropriate. (Evidence supporting this conclusion is of classes:
SIGN (1998)	The decision whether to recommend mastectomy or breast conservation will depe • the ratio of the size of the tumor to the size of the breast: smaller tumors i breasts are more suitable for breast conservation than larger tumors in sr breasts; • the pathological features of the tumor: there is an increased risk of local recurrence if disease (invasive or DCIS) is less than or equal to 1 mm fro margins of excision or at multiple sites; • age of patient: patients aged <35 years are at increased risk of local recu • the patient's own preference; • fitness for surgery and/or radiotherapy. (Recommendation grade C) A central tumor is not a contraindication to conservation although it may neces removal of the nipple and areola, which may compromise cosmesis for some p (Recommendation grade C) If appropriate clinically, women should be offered conservation provided they wish to be involved in decision making. (Recomme grade A)
ACR/ACS/CAP/SSO (1998)	**DCIS.** *Indications for breast-conserving surgery and radiation therapy.* Indications breast-conserving surgery and radiation therapy include DCIS detected mammographically or by physical examination that is localized (without evidence multicentricity or diffuse malignant calcifications). The extent of DCIS should be le

	4 cm because few data exist to support breast conservation's effectiveness in larg lesions. The difficulty in measuring the size of DCIS makes definitive recommend difficult. For mammographically detected DCIS presenting as microcalcifications, all ma calcifications must be removed before radiation is initiated. Negative margins c resection are important to minimize the ipsilateral breast tumor recurrence rate Certain factors preclude the use of radiation in the treatment of patients with D are unrelated to the extent of the disease. These include a history of collagen disease (especially scleroderma and lupus erythematosus), previous therapeu radiation to the breast or chest, and pregnancy. *Indications for breast-conserving surgery alone.* Individual centers have sugge low local recurrence rate for low-grade tumors of small volume excised with cl margins, but the maximum size of DCIS for which radiation therapy could be s omitted is not known. **Stage I and II.** Four critical elements in patient selection for breast-conservatio treatment are history and physical examination, recent mammographic evalua (usually within 3 months), histologic assessment of the resected breast specim assessment of the patient's needs and expectations. Age per se and family his breast cancer are not contraindications to breast conservation. Absolute contraindications include pregnancy (however, in many cases, it may possible to perform breast-conserving surgery in the third trimester and treat th patient with irradiation after delivery); two or more primary tumors in separate quadrants of the breast or with diffuse malignant-appearing microcalcifications history of prior therapeutic irradiation to the breast region that, combined with t proposed treatment, would result in an excessively high total radiation dose to significant volume; persistent positive margins after reasonable surgical attem scleroderma or active lupus erythematosus (in contrast, rheumatoid arthritis is relative or an absolute contraindication). Relative contraindications include history of collagen vascular disease; the pre multiple gross tumors in the same quadrant and indeterminate calcifications; th presence of a large tumor in a small breast in which an adequate resection wo result in significant cosmetic alteration; breast size (women with large or pendu breasts can be treated by irradiation if reproducibility of patient set-up can be a ensured and if 6-MV photon beam irradiation is technically possible to obtain a dose homogeneity). Patients with invasive lobular cancers and those with extensive intraductal cor (EIC) are candidates for conservative surgery and radiation if the tumors can b completely excised with negative margins.
CCOPGI (1996-2000)	**DCIS.** As with invasive disease, there are a number of contraindications for breas conserving surgery. Patients with large tumors (>5 cm) or small breasts may not h satisfactory cosmetic result and may be better served by simple mastectomy with option of reconstruction. The presence of multiple tumors in the breast and the appearance of extensive microcalcifications are also relative contraindications.

	Stage I and II. The presence of multiple tumors in the breast, the appearance mammogram of diffuse malignant microcalcifications, or clinical signs of breas inflammation are contraindications to conservative surgery. Also, when there i extensive intraductal cancer present alone without invasive cancer, total maste without node dissection may be preferable to lumpectomy. If radiotherapy is n accessible or is contraindicated for reasons such as pregnancy, severe heart d disease, or scleroderma, then conservative surgery is generally not recommer the case of pregnancy however, lumpectomy could be carried out with breast irradiation delayed until after delivery. Patients with large tumors (e.g. larger th in diameter) or small breasts may not have a satisfactory cosmetic result and m better served by modified radical mastectomy followed by reconstruction. Whe conservative surgery is contraindicated, the preferred alternative treatment is u modified radical mastectomy. However, for some patients, such as elderly wor those with comorbid medical conditions, total (simple) mastectomy may be a satisfactory alternative. Some patients may decline conservative surgery for p reasons and prefer a modified radical mastectomy.
	Technical Aspects of Surgical Management ***Localization and Assessment of Breast Abnormalities***
ICSI (2000)	For palpable masses, FNA, needle core, or surgical (incisional or excisional) biop be performed. Non-palpable mammographic lesions require radiographic (mamm or ultrasonographic) localization for either core needle or surgical biopsy.
SIGN (1998)	Methods of assessment of a breast abnormality include clinical examination, imag sampling the lesion with a needle for cytological/histological assessment (FNAC o biopsy), which collectively comprise triple assessment. There is strong evidence t assessment provides more accurate diagnosis than a smaller number of tests. (E level IIa) All patients should have a full clinical examination. Where a localized abnorma present, patients should have imaging usually followed by FNAC or core biops lesion considered malignant on either clinical examination, imaging or cytology should have histopathological confirmation of malignancy before any definitive procedure e.g. mastectomy or axillary clearance. (Recommendation grade B) patients with symptomatic disease two-view mammography should be perform part of triple assessment (clinical opinion, imaging and cytology or core biopsy designated breast clinic. Mammography is not recommended under the age of unless there is a strong clinical suspicion of carcinoma. (Recommendation gra Stereotactic or ultrasound guided procedures should be performed on impalpa lesions that are suspicious or equivocal.
ACR/ACS/CAP/SSO (1998)	**DCIS.** DCIS can present as a palpable mass, but this presentation is unusual. Th standards described for palpable invasive disease apply to palpable DCIS. Becau most commonly presents as microcalcifications, image-directed procedures are n for diagnosis and treatment. Stereotactic core-needle biopsy of the breast can be the initial approach for sa suspicious nonpalpable mammographic abnormalities. Ultrasound-guided biop useful for nonpalpable masses but usually cannot be relied upon for biopsy of

	microcalcifications. Nonpalpable, mammographically evident lesions that are excised surgically sh localized presurgically with a guide, such as a guide wire. Any suspicious lesic detected by mammography requires presurgical localization to ensure accurat removal of the abnormal area and to avoid excess sacrifice of breast tissue. **Stage I and II.** *Image-Directed Surgery.* If a patient has a nonpalpable carcino diagnosed by image-guided biopsy or a suspicious lesion detected by mammo then breast-conserving surgery should be conducted with presurgical localizat a guide such as a guide wire. The method of localization may be needle-hook Evans blue dye injection, or a combination of both. **DCIS and Stage I and II.** Frozen-section preparations of tissue obtained from guided needle biopsies of nonpalpable lesions or from mammographically dire biopsies done for microcalcifications are strongly discouraged. Lesions such a atypical ductal hyperplasia, radial scar, and papillary proliferations may be diffi interpret in frozen-section preparations, and small foci of DCIS or microinvasiv carcinoma may be lost or rendered incapable of interpretation by freezing artif Frozen sections should be prepared only when enough tissue is present that t diagnosis will not be compromised (i.e., grossly visible tumors larger than 1.0 when the information is needed for immediate therapeutic decisions.
CCOPGI (1996-2000)	**DCIS.** The management of these lesions requires close cooperation between surg radiologist, and pathologist. At present, the majority of patients with DCIS will be i by mammographic abnormality. A needle or core biopsy may confirm intraductal carcinoma and a preoperative mammogram with magnification views will often de the extent of microcalcifications. In most cases, preoperative localization by the ra will be required using hooked wire or a similar device. Bracketing wires may aid ir marking the extent of the lesion. **Stage I and II.** *Non-palpable Lesions.* With the more widespread use of mammographic screening, more patients are presenting to surgeons with susp mammographic abnormalities but clinically normal breasts. The management lesions requires close cooperation between surgeon, radiologist, and patholog most cases, preoperative localization by the radiologist will be required using h wire or a similar device.
	Technical Aspects of Surgical Management ***Excisional Biopsy and Conservation Surgery (Lumpectomy)***
ICSI (2000)	Biopsy incisions should be placed to minimize subcutaneous tunneling when rem tumor. Whenever possible, an incision should be situated so that it can be remov standard mastectomy incision. Curvilinear incisions following Langer's lines (conc circles around the areola) provide the best cosmesis, especially in the upper hem radial incisions will result in less tissue distortions when larger biopsies are perfor the lower half of the breast. The abnormality should be excised intact with a small rim of normal breast tiss careful orientation for the pathologist. Except in rare and unusual circumstance additional tissue should be removed so that negative microscopic margins are obtained. If additional tissue cannot be removed, patients with focally positive microscopic margins (defined as less than or equal to 3 low powered fields) ca

	considered for breast conserving treatment. In instances of re-excisional biops rim of skin surrounding the incision and the entire biopsy cavity (if the site of in margin(s) unknown) should be removed, orienting the specimen to allow the pathologist to define areas of involved resection margins precisely. Four to six clips at the base of the lumpectomy site will aid in directing the radiation therap and not adversely affect radiologic follow-up. **Stage 0.** Guidelines for lumpectomy for carcinoma in situ are similar to those f invasive cancers requiring all known disease to be removed by clinical, patholo radiographic evaluation. **Stage I.** With rare exceptions, all T1 tumors can be excised with grossly and microscopically clear margins and acceptable cosmesis if the patient desires lumpectomy. Subareolar tumors may require excision of the nipple/areolar cor achieve clear margins. **Stage II.** Similarly, adequate tumor clearance and an acceptable cosmetic res ordinarily be achieved following lumpectomy in patients with larger primary can (Evidence supporting this conclusion is of classes: A, C, D)
SIGN (1998)	Wide local excision is excision of a tumor with a margin of clearance of both invas in situ disease. Lateral margins (histopathological) should be 1 mm or more clear disease. There are no direct comparisons between wide local excision (1 cm mac clearance) with segmental excision (1 cm macroscopic clearance but the excision incorporating tissue from the nipple right out to the periphery of the breast) or quadrantectomy (similar excision to segmental excision but with 2-3 cm macrosco margin clearance). Although indirect comparisons have been performed, the rates recurrence reported are not significantly different. The most important factor relate cosmetic outcome is the volume of tissue excised and therefore quadrantectomie produce less good cosmetic results than wide local excision or segmental excisio The use of specimen radiographs is necessary in the pathology department to histological examination of the appropriate portion of the biopsy specimen. **DCIS.** Localized areas of ductal carcinoma in situ (DCIS) should be excised bo widely and completely pathologically. (Recommendation grade B)
ACR/ACS/CAP/SSO (1998)	**DCIS and Stage I and II.** When breast conservation treatment is appropriate, the any surgical procedure on the breast are total removal of the tissue suspected or be malignant and minimal cosmetic deformity. These goals apply to both diagnos biopsy and definitive local excision. Failure to consider them at all stages may jeo conservation of the breast. *Reexcision of the Biopsy Site:* The previous biopsy site must be re-excised ca ensure negative margins of resection, avoid excess removal of breast tissue, a achieve good cosmesis. If the presence of microcalcifications is in the indicati excision, needle localization should be considered. Proper orientation of the or biopsy specimen avoids the removal of an already adequate margin. When the inadequate margins is not known, a rim of tissue must be removed around the previous biopsy site. **Stage I and II.** *Skin Incision.* Curvilinear skin incisions following Langer's lines

	generally achieve the best cosmetic result. However, in the mid-inner aspect c breast and the lower breast, a radial incision may provide a better result, partic skin removal is necessary. The incision should be over or close to the tumor a adequate size to allow the tumor to be removed in one piece. Periareolar incis inappropriate for lesions in the periphery of the breast. Excision of a segment rarely is necessary and is undesirable because it may alter the position of the the inframammary crease. *Breast Tissue Management.* The primary lesion should be excised with a rim c normal tissue, avoiding excessive sacrifice of breast tissue. Tumors in the sub area may require excision of the nipple-areolar complex to ensure adequate tu margins and to avoid devascularization. The surgeon should approach lesions the substance of the breast by incising the overlying breast tissue. Meticulous hemostasis is critically important. Drains in the breast should be avoided. The specimen must be oriented with the use of sutures, clips, multicolored ind ink, or another suitable technique; the specimen should not be sectioned befo submitted to the pathologist. Any uncertainty regarding orientation of the speci should be clarified for the pathologist by the surgeon. Clips outlining the breas may aid the planning and execution of radiation therapy and demarcate the tu for future imaging studies. The specimen should be examined for the determin a grossly clear margin. If a clear margin is not evident, the tumor should be re- at that time. Routine frozen section evaluation of margins is optimal and does guarantee negative margins after a complete examination. *Reexcision of Biopsy Site:* The surgeon must reexcise the previous biopsy site carefully to ensure negative margins of resection, to avoid excess breast tissu removal, and to achieve good cosmesis. When the site of inadequate margins known, a rim of tissue must be removed around the previous biopsy site. A sm segment of skin incorporating the biopsy site should be removed, and underm should be kept to a minimum. For larger biopsy cavities, shaving of each indiv margin and marking of the new margin surface allow the surgeon to remove re tumor while preserving a maximum amount of breast tissue. For very small ca removal of the entire biopsy site as an en bloc specimen is acceptable. **DCIS and Stage I and II.** *Specimen Radiograph:* A radiograph of the specime be obtained, preferably in two dimensions (orthogonal projections). The specir should be correlated with a preoperative mammogram and interpreted without The radiologist's report should indicate whether the mammographic abnormali of calcifications) is seen in the specimen and if it has been removed completel as can be determined. The proximity of the abnormality to the edge of the rese tissue should be noted. Absence of the mammographic abnormality on the spe radiography usually indicates that it has not been removed. If the diagnosis of extension of calcification (or mass) to the margin of the specimen suggests tha residual tumor might be present in the breast and that further resection along t margin may be indicated.
CCOPGI (1996-2000)	**DCIS.** Complete excision of the lesion should be achieved. Studies have shown t positive or indeterminate resection margins increase the risk of local recurrence. specimen radiograph is essential to ensure that the lesion has been excised. Car pathological assessments of margins, as well as presence of comedo necrosis ar should be determined as these factors are predictive of risk for recurrence. When microcalcifications are present, a postoperative mammogram should be performe

	confirm complete excision. If the excision has been incomplete, a re-excision sho carried out. **Stage I and II.** Patients with operable breast cancer present to their surgeon e with a palpable lesion in the breast or an abnormal mammogram with a clinica normal breast. The appropriate management differs somewhat in these two sit *Palpable Lesions:* Any suspicious breast lump should be completely excised th cosmetically acceptable incision placed directly over the mass, i.e., the breast should actually be a lumpectomy. The aim of lumpectomy is to completely exc lesion along with a margin of normal breast tissue to ensure complete removal is no firm consensus on the extent of resection. There is a suggestion that loca recurrence rates were lower in the studies where quadrantectomy was perform in studies of lumpectomy. A larger incision may reduce the incidence of local recurrence but at the expense of cosmesis. Radial incisions should not be per in the upper quadrants. The specimen should be given intact (i.e., not bisected to the pathologist for inking of the margins, frozen section confirmation and est receptor assay. No deep sutures should be placed in the wound, and a drain s not be inserted; the best cosmetic result is achieved by subcuticular sutures. *Non-palpable Lesions.* Complete excision of the lesion should be achieved. Sp radiography is essential to ensure that the lesion has been excised. As a rule, section should be avoided since the amount of tissue may be limited and prec pathologic diagnosis would be difficult.
	Technical Aspects of Surgical Management ***Pathologic Evaluation of Breast Tissue***
ICSI (2000)	Biopsy report is reviewed and if cancer is present staging is initiated. Pathologic r recommendations include: • Tumor size • Margin status • Node number and involvement • Proportion of invasive and in-situ component to determine presence of EI • Histologic grade (indicate grading system utilized) • Nuclear grade (indicate grading system utilized) • Histologic subtype • Presence of multifocal disease: gross and microscopic • Lymphatic or vascular invasion • Necrosis • ER/PR
SIGN (1998)	The nature of specimens to the pathologist varies widely, depending on surgical p and protocols of management. The pathological report of cancers diagnosed in ex specimens should include the following minimum detail: GROSS: BREAST • Side of origin, nature of specimen and whether appropriately orientated; i biopsy, does x-ray indicate suspect area?

	• Dimensions of specimen: mm measurement in maximum or three dimens as specimen weight in grams (or both) • Characteristics and dimensions of any grossly identifiable lesion, mm measurement in maximum, or three dimensions • Relation of lesion to nearest margins (specified), noting particularly if lesi extends into gross margins (cut through) GROSS: LYMPH NODES • Nature of specimen (sample, clearance, other nodes) • Total number of lymph nodes processed MICROSCOPY: BREAST • Specify whether cancer is noninvasive or invasive • Noninvasive only cancer should be described according to its histological and its nuclear grade (low, intermediate, high) • Noninvasive cancer should be estimated for its extent (in mm) and relatio nearest margin (specified in mm) • Invasive cancers should be measured (in mm) and noted if different from Special types should be identified and all types should be graded (stating • State margin and relationships as 'reaches, uncertain or (specified) neare mm' • Comment on whether disease is 'localized, multiple or with satellites' • Comment on presence or absence of lymphatic/vascular invasion. • Determine oestrogen receptor status by immunohistochemistry MICROSCOPY: LYMPH NODES • State total number confirmed and number with metastasis • Specify node(s) where metastasis is microscopic (less than one mm) or s
ACR/ACS/CAP/SSO (1998)	**DCIS and Stage I and II.** The pathologist includes certain basic data in each surg pathology consultation report because the data are important prognostically or are for staging or therapy. The following features should be included in the surgical pa consultation report: • How the specimen was received (e.g., number of pieces, fixative, orientat • Laterality and quadrant of the excised tissue and the type of procedure, a specified by the surgeon • Measured size of the tumor (in three dimensions if possible) • Histologic type and grade (including histologic features of DCIS, e.g., nuc grade, necrosis, architectural pattern) • Presence or absence of coexistent DCIS or an extensive intraductal comp • Presence or absence of peritumoral angiolymphatic invasion • Presence or absence of gross or microscopic carcinoma (either invasive carcinoma or DCIS) at the margins of excision; if possible, the distance o tumor or biopsy site from the margin should be stated • Lymph node status, including the number of lymph nodes found in the sp the number of involved nodes, the size of the largest involved node, and t

	presence or absence of extension beyond the lymph node capsule Determination of estrogen and progesterone receptors is standard for invasive carcinomas. This can be done either by the traditional ligand-binding assays p on sample frozen tissue or by immunohistochemistry performed on routinely fi tissue sections. The results of ancillary studies (such as steroid receptors anal DNA ploidy, proliferative rate, and so forth are usually reported in an addendu supplement to the surgical pathology report.
CCOPGI (1996-2000)	**DCIS.** Careful pathological assessment of margins, as well as presence of comed necrosis and grade, should be determined as these factors are predictive of risk f recurrence. When microcalcifications are present, a postoperative mammogram s performed to confirm complete excision. If the excision has been incomplete, a re can be carried out. **Stage I and II.** <u>Palpable Lesions</u> Specimens should be given intact (i.e., not bisected) directly to the pathologist inking of the margins, frozen section confirmation and estrogen receptor assay <u>Non-palpable lesions</u> If insufficient material is available for estrogen receptor assay by bioassay, the estrogen receptor assay using the ERICA method should be performed on pa sections.
	Technical Aspects of Surgical Management ***Mastectomy***
ICSI (2000)	For mastectomy, if only cytologic diagnosis (e.g., fine needle aspirate (FNA) spec cancer has been obtained, a histologic specimen to prove the diagnosis should b considered before proceeding with mastectomy. A transverse or obliquely-oriente elliptical incision should be used, encompassing the biopsy skin incision wheneve possible. Peripherally located biopsy sites may need to be excised separately. Th areolar complex and all apparent breast tissue should be excised. Tumor involver the chest wall must be documented, widely excised and marked with clips to direc postoperative radiation therapy. Reconstruction should be offered to women with Stage 0-II breast cancer who or desire mastectomy. (Evidence supporting this conclusion is of class: R) If th is considering reconstruction, a referral to a plastic surgeon is indicated. When immediate reconstruction is to be performed by a plastic reconstructive the general surgeon should complete the extirpative procedure without compr oncologic surgical principles. Skin-sparing mastectomies are appropriate as lo there is an adequate anterior margin around the tumor and the previous biops is excised with the specimen. Injuries to the neurovascular bundles or fascial p the chest wall that are to be utilized in reconstruction should be avoided. Implants/expander placement or free tissue transfer procedures can be used f immediate reconstruction. Cosmesis will be less satisfactory in patients who w receive post-mastectomy chest wall irradiation. (Evidence supporting this conc of class: C)

SIGN (1998)	Mastectomy is indicated for operable breast cancer which is either large or at mul sites, when radiotherapy is to be avoided, or by patient preference. A modified rad mastectomy removes all breast tissue and axillary nodes, and avoids the need for radiotherapy in most cases. High grade tumors with lymphatic permeation and mu axillary node involvement are associated with significantly higher risk of locoregio recurrence which can be reduced by radiotherapy. When mastectomy is carried o axillary clearance is usually performed. The possibility of breast reconstruction sh discussed with all patients prior to mastectomy. (Recommendation grade C) In patients with extensive DCIS (over 4 cm) or disease affecting more than one quadrant a mastectomy should be performed. (Recommendation grade B)
ACR/ACS/CAP/SSO (1998)	**DCIS.** Although many women with DCIS are candidates for breast-conserving tre with or without irradiation, in some patients mastectomy is clearly indicated. Such include women with two or more primary tumors in the breast or with diffuse, mali appearing microcalcifications and those with persistent positive margins after reas surgical attempts. In addition, for some women the risk:benefit ratio of breast conservation must carefully assessed, and consideration must be given to mastectomy as a treat alternative. Neither tumor size nor histologic type of DCIS is an absolute indication for mastectomy. However, a relative indication for mastectomy is the presence of extensive DCIS that can be removed with only a small negative margin. This is particularly true in a patient with a small breast in which an adequate resection result in a significant cosmetic alteration that is unacceptable to the patient. **Stage I and II.** Patients with EIC positive tumors in whom the initial margins of resection are positive should undergo re-excision. If the re-excision margins ar negative, current information would suggest that these patients are appropriate candidates for conservative surgery and radiation. If the re-excision margins re positive, mastectomy is the preferred treatment.
CCOPGI (1996-2000)	**DCIS.** Mastectomy with the option for reconstruction remains an acceptable choic women preferring to maximize local control. **Stage I and II.** Modified radical mastectomy is considered for those patients in for breast conservation therapy (see Conservation Surgery Eligibility above) ar those who decline conservative surgery for personal reasons.
	Technical Aspects of Surgical Management ***Axillary Surgery***
ICSI (2000)	When axillary dissection is performed as part of a breast preservation operation, t procedure should usually be undertaken through a separate incision, preferably a transverse curvilinear incision within the anterior and posterior axillary folds rather vertical incision. In select and unusual cases, a separate incision may not be requ these cases, the location of the primary tumor permits it to be excised through an placed posterior to the anterior axillary line. This same incision can also be used f performing the axillary dissection.

	In any axillary dissection, all grossly involved lymph nodes should be excised l tissues surrounding the axillary vein anteriorly and posteriorly should be left in lessen the risk of lymphedema. All tissue caudad to the axillary vein and latera medial border of the pectoralis minor should be excised. Injury or intentional transection for improved nodal clearance of the medial pectoral, long thoracic, thoracodorsal nerves should be exceedingly rare. At completion of axillary dis a closed-system suction drainage catheter should be placed. Axillary dissection is not necessary for intraductal carcinoma in situ (DCIS). Axillary dissection includes Level I and Level II lymph node regions. The surge advised to remove all grossly evident disease if possible. Lymph nodes fixed t another or other structures are classified as N2 disease, making the tumor Sta greater. These findings should be included in the operative report. **Stage 0.** In large (greater than or equal to 2.5 cm) non-invasive carcinoma, es those with comedocarcinoma features or palpable lesions, invasive foci may b present. Consideration of axillary nodal sampling or partial axillary dissection s given in these instances. **Stage I.** Axillary dissection is routinely performed for clinical Stage I cancers p for staging purposes. In rare instances of small low grade cancers (i.e., tubula carcinoma < 1 cm), particularly in elderly or debilitated patients with a benign a exam, axillary dissection may be omitted. **Stage II.** Axillary dissection is routinely performed for Stage II breast cancers f staging the disease and regional control of tumor. (Evidence supporting this co is of classes: C, R) <u>Sentinel Nodes</u> Axillary lymphadenectomy remains the standard of practice with invasive brea cancer. Sentinel lymph node biopsy is an evolving technology and shows a hig degree of accuracy in staging the axilla, given sufficient surgeon experience.

SIGN (1998)	Axillary surgery should be performed in all patients with invasive operable breast (Recommendation grade B) There is no consensus as to the best way to manage axilla in patients with invasive carcinoma. The following procedures have been pr
	
	• Axillary node sampling: picking out at least four individual lymph nodes fr lower axillary fat. This stages the axilla, but is not a form of treatment.
	• Axillary node clearance: a block dissection of the axillary contents:
	  • level I is up to the lateral border of pectoralis minor
	  • level II is up to the medial border of pectoralis minor
	  • level III is up to the apex of the axilla
	
	Only level III dissection fully stages the axilla and treats nodal disease. Furthe treatment of the axilla may be required for patients who have had a level I or I dissection if involved nodes are identified histologically. Further treatment afte dissection is only considered if the nodes cannot be adequately cleared or if th extranodal spread of tumor.

	For larger tumors (T2 and above) a complete level III axillary clearance should considered. After axillary sampling, the axilla should only be irradiated if node or inadequately sampled. (Recommendation grade A) After axillary clearance, axilla should not normally be irradiated. (Recommendation grade B) For patients with DCIS, surgical staging of the axilla is not required. (Recomm grade B) <u>Sentinel Nodes</u> A procedure that is currently being evaluated is sentinel node biopsy but until r from larger series are available, this cannot yet be recommended for routine p
ACR/ACS/CAP/SSO (1998)	**DCIS.** Axillary node metastases are uncommon in DCIS. Axillary dissection is not necessary for the management of most patients with DCIS. Unsuspected invasive or microinvasive carcinoma occurs more frequently in association with extensive DCIS of high nuclear grade. Most of these patients mastectomy to encompass the disease. Therefore, a low axillary sampling or l dissection performed when the mastectomy is done avoids a second operative procedure if invasive carcinoma is found in the mastectomy specimen. If a clin suspicious node is found during surgery, a frozen section should be done, and node is positive, a level I and II axillary node dissection should be performed. **Stages I and II.** Patients with positive axillary nodes do not have an increased breast recurrence when treated with conservative surgery and radiation. This i contrast to patients undergoing mastectomy where the number of positive axill nodes correlates with the incidence of chest wall recurrence. The breast incision and axillary incision should be separate. The exception ma axillary tail tumor that can be readily removed through the axillary incision. For tumors that are 1 cm. or less in diameter and tumors of a favorable histologic t tubular, mucinous, papillary), removal of Level I nodes is adequate. For stagin purposes, removal of Level I and Level II nodes permits an accurate assessm axillary nodal status. Removal of Level III nodes is advised only when encomp obvious disease is necessary. The thoracodorsal and long thoracic nerves should be preserved. The medial nerve also should be preserved. Preservation of the intercostal brachial nerve desirable, but may not be possible if preservation compromises adequate exci grossly positive or suspicious nodes. Circumferential stripping of the axillary ve unnecessary and may increase the incidence of edema. Closed suction draina advisable. Exercise may be prescribed early in the postoperative period. Early postoperative exercise may prolong axillary drainage, but it prevents frozen sh Shoulder immobilization with arm slings and wraps should be avoided. <u>Sentinel Nodes</u> Sentinel node lymphatic mapping is still considered investigational.
CCOPGI (1996-2000)	**DCIS.** With respect to the need for axillary dissection, retrospective data suggest incidence of occult microinvasion and positive nodes relates to the size of the prir lesion. Microinvasion is unlikely in lesions <5 cm, and axillary dissection is not ind

	Stage I and II. Patients with operable breast cancer present to their surgeon e with a palpable lesion in the breast or an abnormal mammogram with a clinica normal breast. The appropriate management differs somewhat in these two sit *Palpable Lesions:* Ipsilateral lymph node dissection to include removal of level axillary lymph nodes should be carried out in most cases of Stage I and II brea carcinoma. When palpable axillary lymph nodes suggestive of axillary metasta noted on clinical examination, axillary dissection should be carried out. The pri purpose for axillary dissection in clinically node-negative patients is completior staging process, in order to predict the necessity for adjuvant systemic or loco therapy, and to assess the prognosis. The secondary purpose is therapeutic, i to reduce region axillary recurrence of disease. At present, there is insufficient evidence to justify the omission of axillary dissection on the basis of primary tu alone. Axillary dissection might be omitted if the patient is clinically node nega because of severe underlying comorbid conditions, would not benefit from the surgery, or if therapeutic decision making, in terms of adjuvant therapy, would altered (this may be particularly relevant in the elderly patient). If omission of a dissection is being considered, the patient should be aware of the rationale an axillary dissection as an alternative. Axillary surgery is not required in patients ductal carcinoma in situ (DCIS). There is controversy about further manageme the pathologist reports microscopic involvement of the margins of resection wi invasive cancer or DCIS. These patients are at increased risk for a local recur and re-excision or total mastectomy should be seriously considered. (This doe apply to lobular carcinoma in situ at the margins.) The patient should be inform the margins are positive. The efficacy of a radiation boost to the tumor site is u *Non-palpable Lesions:* Further management should be deferred until the patho has carefully studied the permanent sections. If the excision has been incomp re-excision can be carried out, and an axillary lymph node dissection should b performed through a separate incision for all patients with invasive cancer. Ste core needle biopsy has recently been used in the diagnosis of nonpalpable les this procedure does not obviate the need for excisional biopsy in all circumsta <u>Sentinel Nodes</u> No recommendations offered.
	Radiation Therapy (XRT) ***Post-Conservation Surgery***
ICSI (2000)	At this time, no Stage I or Stage II subgroups have been defined in which XRT the can be omitted. If the patient is on a protocol, then follow the protocol specifics as delivery of radiotherapy. Otherwise the following recommendations are made. If chemotherapy is not to be given, XRT should be started in a timely fashion (within 2-4 weeks). XRT may be delayed if significant seroma is present, if a ce present, if arm range of motion is still limited, or if incisions are not healed. The way to integrate XRT and chemotherapy in patients who are to receive both is well defined. The two modalities have been given concurrently, sequentially, o sandwich fashion (i.e., chemotherapy both prior to and after XRT). In Stage II, or a portion of chemotherapy is given initially. Megavoltage XRT is recommended to the whole breast using tangential fields

	bolus) treating to a dose of 4500-5000 cGy (180-200 cGy per fraction) over a 4 1/2 week period. This is usually followed by a boost of XRT to the area of the excisional biopsy for an additional 1000 to 2000 cGy. Omission of the boost m associated with an increased risk of breast recurrence in patients with focally p microscopic margins or unknown marginal status. In patients with negative ma resection, the role of boost XRT is not fully defined, but the boost has usually b performed. Placement of surgical clips within the excisional biopsy site is encouraged in o aid in improving XRT portal localization. In general, regional (lymph node) radiotherapy is not usually performed after conservative surgery including a level I/level II axillary lymph node dissection. positive axillary lymph nodes are found at the time of lymph node dissection, r radiotherapy is not recommended. Regional radiotherapy is controversial for p with ≥4 positive axillary lymph nodes, a positive high axillary lymph node, extra disease extension, or a large axillary lymph node; or if <6 lymph nodes were re from the axilla. Regional XRT is never recommended for stage 0 disease. Whe regional XRT includes the supraclavicular area axillary area and not usually th internal mammary area. If regional radiotherapy is given to the supraclavicular or internal mammary areas, a dose of 4500 to 5000 cGy over a 4 1/2 to 5 1/2 w period is recommended. Special care must be taken in matching the supraclav field with the tangential breast fields. In the rare instance where internal mamm radiotherapy is recommended, a portion of the course should be given with an beam. When using deep tangential fields to treat the breast and internal mamm area, care must be taken to limit the amount of heart and lung within the fields (Evidence supporting this conclusion is of classes: A, C, D, R)
SIGN (1998)	Radiotherapy should normally be given to the breast after wide local excision. (Recommendation grade A) For patients with small well-differentiated invasive carcinomas, an axillary nod is required to determine nodal status; consider entering patients into clinical st radiotherapy and tamoxifen (BASO-II study); and for patients outside a clinical wide local excision should be combined with radiotherapy and systemic therap appropriate. (Recommendation level C) Following adequate local excision of DCIS, patients should be considered for radiotherapy to the breast. (Recommendation grade C) *Radiotherapy after surgery to the axilla:* After axillary sampling, the axilla should only be irradiated if node positive or inadequately sampled. (Recommendation grade A) After axillary clearance, the axilla should not normally be irradiated. (Recomm grade B)
ACR/ACS/CAP/SSO (1998)	**DCIS and Stage I and II.** Radiation therapy should be delivered only after evalua the mammography findings, the pathology findings, and the surgical procedures performed on the patient. The optimal combination of surgery and irradiation is determined by the extent, nature, and location of the tumor; the patient's breast si

	the patient's relative concerns about local recurrence and preservation of cosmeti appearance. A consensus exists regarding some, but not all, of the elements in the techniq irradiation. As soon as the patient has healed adequately from the surgical pro radiation therapy should begin (usually within 2 to 4 weeks after uncomplicate conserving surgery). The radiation oncologist should use measures to ensure reproducibility of pati up, treatment stimulation, treatment planning, and choice of supervoltage equi for dose homogeneity. Higher energy photons (10 MV or more) may be indicat large-breasted women or patients with significant dose inhomogeneity (10% o when lower energy photons are used. The radiation oncologist can use sophisticated treatment planning that involve dimensional rather than two-dimensional dose distributions and accounts for t density of lung tissues in the treatment field. (In standard treatment planning, t is considered to have unit density.) Currently, three-dimensional dose distribut not considered standard. Each field should be treated on a daily basis, Monday through Friday. A bolus not be used. To minimize the risk of radiation pneumonitis, not more than 3.0 t of lung (as projected on the radiograph at isocenter) should be treated, and a r of 1.0 to 1.5 cm of lung is required. For left-sided lesions, efforts should be ma minimize the amount of heart in tangential fields. Whole-breast radiation thera delivered using opposed tangential fields to a dose of 4,500 to 5,000 cGy at 18 cGy per fraction. Controversy exists about the need for delivering an additional boost dose to th primary site. Although boost irradiation often is used, the precise indications fo are not well defined. When used, boost irradiation is delivered using electron b interstitial implantation. The total dose to the primary tumor site is increased to approximately 6,000 to 6,600 cGy. A boost may not be required for patients wh been treated with more extensive breast resections and have margins of re-se that are clearly negative. If the breast boost is omitted in these patients, the or available data indicate that the standard whole-breast radiation therapy is 5,00 200 cGy per fraction. *Techniques to avoid* (**DCIS**) Nodal irradiation is unnecessary, and excess dose to the heart or lungs throug tangential irradiation of the breast must be avoided. *Techniques to avoid* (**Stage I and II**) Axillary irradiation usually is unnecessary following a complete axillary dissecti (Levels I to III). Irradiation of the supraclavicular fossa and the contiguous apic may be considered if a large number of lymph nodes (4 or more) contain tumo benefit of radiation in patients with 1 to 3 positive nodes is unknown. Overlap b adjacent fields should be avoided.
CCOPGI	**DCIS.** Women who have undergone breast conserving surgery should be offered

(1996-2000)	postoperative breast irradiation. Women with small (less than 2.5 cm) well differe tumors that are fully resected with clear margins (greater than 10 mm) should cor participating in clinical trials exploring radiation versus wide excision alone. **Stage I and II.** Women with early stage (Stages I and II) breast cancer who ha undergone breast conserving surgery should be offered postoperative breast irradiation. The optimal fractionation schedule for breast irradiation has not been establish the role of boost irradiation is unclear. It is recommended that patients particip ongoing clinical trials evaluating different fractionation schedules. Outside of a clinical trial, two commonly used fractionation schedules are sugg 50 Gy in 25 fractions to the whole breast, or 40 Gy in 16 fractions to the whole with a local boost to the primary site of 12.5 Gy in five fractions. Shorter sched e.g., 44 Gy in 16 fractions or 40 Gy in 16 fractions have also been used routin some centers. There are no randomized trials that demonstrate inferior efficac schedules. Women who have undergone breast conservation surgery should start local br irradiation as soon as possible following wound healing. A safe window betwe surgery and commencement of radiation is unknown, but it is reasonable to sta irradiation within 12 weeks of definitive surgery. For patients who are candidates for chemotherapy the optimal sequencing of chemotherapy and radiation is not known. It is reasonable to institute radiation following completion of chemotherapy or concurrently when anthracycline-con regimens are not used.
	Radiation Therapy ***Post-Mastectomy***
ICSI **(2000)**	If a patient is on a protocol which requires postoperative XRT, the XRT should be delivered according to the protocol specifics. Otherwise the following recommend are made. Concerning the integration of post-mastectomy XRT and chemotherapy, a spe sequencing recommendation cannot be made. The two modalities have been combined in a number of ways, although often all or a portion of chemotherapy initially. Megavoltage XRT with a tangential field setup or an electron beam technique recommended for treatment of the chest wall region itself to a total dose of 45(5000 cGy (180 to 200 cGy per fraction) over a 4 1/2 to 5 1/2 week period. A bo 1000 to 1500 cGy to the area of the primary site and/or chest wall scar region often performed. XRT should be delivered so as to minimize areas of dose nor uniformity within the treatment volume (e.g., use of appropriate energies, wedg compensators, and tissue bolus) and the volume of lung and heart receiving a significant dose of radiation. In addition to chest wall XRT, radiation therapy to the supraclavicular area is u performed. Consideration must also be given to the need for axillary and intern

	mammary XRT. The total dose delivered to the regional lymph node areas is approximately 4500 to 5000 cGy over a 4 1/2 to 5 1/2 week period. Special ca be taken in matching the supraclavicular field with the tangential or electron be chest wall fields. The internal mammary field should be given with at least a pc using an electron beam. In addition, if using deep tangential fields to treat the wall and internal mammary area, care must be taken to limit the amount of hea lung within the fields. (Evidence supporting this conclusion is of classes: A, C,
SIGN (1998)	Radiotherapy should be given to the chest wall after mastectomy in those patients to be at high risk of local recurrence. (Recommendation grade A) *Radiotherapy after surgery to the axilla:* After axillary sampling, the axilla should only be irradiated if node positive or inadequately sampled. (Recommendation grade A) After axillary clearance, the axilla should not normally be irradiated. (Recomm grade B)
ACR/ACS/CAP/SSO (1998)	No recommendations offered.
CCOPGI (1996-2000)	No recommendations offered.
	Adjuvant Systemic Therapy (Chemotherapy, Endocrine therapy)
ICSI (2000)	Treatment options in women with Stage I-II disease who are ER positive or PR pc include chemotherapy* + tamoxifen. In women with Stage I-II disease who are ER negative, PR negative, chemoth alone or observation is recommended. *Note: Chemotherapy may be advised for women up to age 70 if the patient's anticipated life expectancy is >10 years. Chemotherapy should be administered by experienced physicians and/or pers using established chemotherapy protocols and guidelines for dosage modifica Patients should be encouraged to enter clinical trials. **Stage 0.** Adjuvant chemotherapy is not advised. **Stage I.** Currently accepted chemotherapeutic regimens in node-negative brea cancer include: • Cyclophosphamide/doxorubicin/5 fluorouracil x 6 cycles • Cyclophosphamide/methotrexate/5 fluorouracil x 6 cycles • Doxorubicin/cyclophosphamide x 4 cycles • Methotrexate/leukovorin/5 fluorouracil x 6 cycles

	Stage II. Currently accepted chemotherapeutic regimens outside of clinical tria include: • Cyclophosphamide/methotrexate/5 fluorouracil x 6 cycles • Cyclophosphamide/doxorubicin/5 fluorouracil x 6 cycles • Doxorubicin/cyclophosphamide x 4 cycles • Doxorubicin x 4 cycles followed by cyclophosphamide/methotrexate/5 fluo x 8 cycles • Doxorubicin/cyclophosphamide X 4 cycles, followed by 4 cycles of paclita Alternative regimens are not advised outside of clinical trials.
SIGN (1998)	All women with invasive breast cancer should be considered for adjuvant systemi therapy. (Recommendation grade A) Patients should be entered into clinical trials possible. (Recommendation grade C) Adjuvant systemic therapy should be determined by an assessment of the wor risk of recurrence (based primarily on node status, histological grade and tumo ER status of the primary tumor and her menopausal status. (Recommendation A) Adjuvant systemic therapy should be determined by a team including the surg oncologist, breast care nurse and pathologist, and in discussion with the patie (Recommendation grade C) **Standard treatments:** (In the following, *low risk disease* is defined as mostly node negative, and *intermediate or high risk disease* as node positive or nega grade 3 or 3 tumors.) Pre- or peri-menopausal women: • Women with low risk disease should be considered for tamoxifen if ER po (Recommendation grade A) • Women with intermediate or high risk disease who are ER positive should offered chemotherapy or ovarian ablation. (Recommendation grade A) • Women with intermediate or high risk disease who are ER negative shou offered adjuvant chemotherapy. (Recommendation grade A) Post-menopausal women: • Women with low risk disease should be considered for tamoxifen if ER po (Recommendation grade A) • Women with intermediate or high risk disease and ER positive tumors sh considered for tamoxifen and/or CMF. (Recommendation grade A) • Women with intermediate or high risk disease and ER negative tumors sh fit, be considered for CMF chemotherapy (tamoxifen). (Recommendation C) *Chemotherapy* The most widely used chemotherapy regimen is a combination of CMF. Outsid

	trials standard adjuvant chemotherapy should usually be CMF (given for six cy (Recommendation grade A). An anthracycline-based regimen should be consi women at high risk of relapse, preferably in the context of a clinical trial (Recommendation grade A). Other cytotoxic regimens, including high-dose chemotherapy, should normally be used only within clinical trials. (Recommen grade C) Chemotherapy should be prescribed by oncologists and administered by spec nurses with appropriate pharmacy support. (Recommendation grade C) *Endocrine therapy* Tamoxifen should be given at a dose of 20 mg/day for at least five years unles treatment is being given in a clinical trial. (Recommendation grade A) Tamoxif benefits apply to women of all ages but are largely confined to women with ER (or ER unknown) tumors. (Evidence level Ia) Ovarian ablation should only be considered for pre-menopausal women with E positive tumors. (Recommendation grade A) The effect of ovarian ablation (eit radiotherapy, surgery or drug therapy) is similar to that of chemotherapy in wo aged less than 50. These effects appear to be limited to women with ER positi tumors. (Evidence level Ia and Ib) Endocrine treatments (other than tamoxifen and ovarian ablation) should be administered only within a clinical trial. (Recommendation grade C)
ACR/ACS/CAP/SSO (1998)	**DCIS.** Until more data become available, the use of tamoxifen outside a clinical tr appropriate. **Stage I and II.** No recommendations offered.
CCOPGI (1996-2000)	**DCIS.** While there is some evidence to suggest that tamoxifen is effective in the r of ipsilateral recurrence and contralateral incidence, the absolute benefit should b weighed against the small risk of developing endometrial cancer. **Stages I and II.** A patient with node-negative breast cancer should be informe availability of adjuvant systemic therapy and should be offered the opportunity discussing such therapy with an expert clinician. She should be provided with information concerning her risk of recurrence if untreated, the potential efficac adjuvant therapy in terms of recurrence and mortality, and the potential side ef therapy. *Choice of therapy:* • Pre- and postmenopausal women at minimal or low risk of recurrence (<2 well-differentiated and all other factors favorable or <1 cm, intermediate g all other factors favorable) should receive no adjuvant systemic treatment should however be made aware that systemic therapy is offered to wome higher risk of recurrence. • Premenopausal women (age <50 years) at moderate risk of recurrence (1 and intermediate grade, or 2-3 cm and well-differentiated) and with ER po tumors should be offered tamoxifen. If the patient refuses tamoxifen,

	chemotherapy may be considered. Chemotherapy added to tamoxifen ma provide a modest incremental benefit over tamoxifen alone. This is an ide situation for a decision aid. • Premenopausal women (age <50 years) at high risk of recurrence (>3 cm irrespective of any other factors, or >1 cm with either ER negative, high g lymphatic/vascular invasion) should be offered chemotherapy. There are insufficient data at the present time to recommend the addition of tamoxif chemotherapy in this subgroup. If the patient refuses chemotherapy and t ER positive, tamoxifen may be considered. There is insufficient data to de the risk category of a tumor <1 cm in diameter associated with a poor pro factor (e.g., grade III, estrogen-receptor-negative, lymphatic/vascular inva • Postmenopausal women (age >50 years) at high risk of recurrence (>3 cr cm with high grade or lymphatic/vascular invasion) and with ER positive t should be offered tamoxifen plus chemotherapy. The benefits and risks o additional chemotherapy should be discussed with the patient. If the patie refuses chemotherapy, then tamoxifen alone should be considered. Postmenopausal women at high risk of recurrence and with ER negative should be offered chemotherapy. • Postmenopausal women (age >50 years) at moderate risk of recurrence (and intermediate grade, or 2-3 cm and well-differentiated) and with estrog receptor-positive tumors should be offered tamoxifen. Chemotherapy adc tamoxifen may provide a modest incremental benefit over tamoxifen alon an ideal situation for the use of a decision aid. *Chemotherapy* For patients who are candidates for chemotherapy, the optimal sequencing of chemotherapy and radiation is not known. It is reasonable to institute radiation following completion of chemotherapy or concurrently when anthracycline-con regimens are not used. Polychemotherapy should reasonably comprise six cycles of CMF or four cycl *Endocrine therapy* Hormonal therapy should consist of oral tamoxifen 20 mg daily for five years.
	Neoadjuvant therapy
ICSI (2000)	Patients with biopsy-proven invasive breast cancer may be eligible for neoadjuva surgical) systemic therapy clinical trials. For selected patients, neoadjuvant chem may make breast conservation feasible. For Stages I and II, this approach is not recommended outside the auspices of a formal clinical trial.
SIGN (1998)	**Definition:** Neoadjuvant chemotherapy is the administration of chemotherapy to with non-metastatic primary breast cancer which is potentially operable. On comp chemotherapy, patients would normally proceed to definitive surgery with or witho radiotherapy. Since chemotherapy is given prior to surgery, the diagnosis should be confirm formal biopsy (e.g. a Tru-cut), as a positive FNA could be due to DCIS rather t invasive cancer. There are limited trial data, but these show that neoadjuvant

	chemotherapy downstages the patients and may allow more patients to have lumpectomy rather than mastectomy, but there is no advantage in terms of dis free or overall survival. Neoadjuvant chemotherapy should normally be followe surgery, even when a complete clinical response is obtained. Neoadjuvant chemotherapy should be given, where possible, within clinical trials. (Recomm grade C) Some patients with larger T2 (>3cm) or T3, N0 or 1, M0 may be considered fo systemic therapy (neoadjuvant) prior to surgery.
ACR/ACS/CAP/SSO (1998)	No recommendations offered.
CCOPGI (1996-2000)	No recommendations offered.
	Follow-Up Care
ICSI (2000)	This recommendation for follow-up refers only to the asymptomatic patient. New c persistent symptoms must be evaluated using whatever diagnostic studies are appropriate. **Stage 0.** Annual mammography, history and physical examination are recomn No other routine laboratory or x-ray studies are recommended for patients with history of treated Stage 0 breast cancer. (Conclusion Grade: I) **Stage I and Stage II.** Patients who have Stage I or Stage II breast cancer sho followed with yearly mammography. Clinical breast examination should be per every 3–4 months for 2 years, then every 6 months for 3 more years. Thereaft medical care should be rendered according to routine health recommendation (Conclusion Grade: I) **Note:** The use of chest x-rays, serum chemistries, bone scans, and soluble tu markers are not indicated for the routine follow-up of patients with Stage 0, I o breast cancer and are not recommended outside of clinical trials.
SIGN (1998)	Routine follow-up screening for distant metastases in asymptomatic women shou performed. (Recommendation grade A) Mammograms of the treated breast should be performed one year after treatm give a baseline for future comparison; and every 1-2 years thereafter. (Recommendation grade B) Clinical examination of the contralateral breast should be carried out at each c and mammography every 1-2 years. (Recommendation grade B) The optimal regimen for frequency of follow up has not been defined. A pragm schedule would be for patients to be seen every six months for the first two ye annually thereafter, with regular mammography scheduled as above.
ACR/ACS/CAP/SSO	The evaluations outlined in the following sections should be done by the physicia

(1998)	cited intervals after treatment is completed. *History and physical examination* (**DCIS**) The frequency of examination, which is based on optimal timing for identificati local recurrence and second primary tumors, is as follows: every 6 months, ye 5 (some oncologists prefer every 6 months until after year 8, when the risk of l recurrence with breast-conservation treatment begins to approach the risk of contralateral breast cancer); annually thereafter. *Physical Examination* (**Stage I and II**) Local failure occurs at a constant rate in the time interval; therefore, frequency examination should be based on risk factors for both local and distant recurrer intervals for examination are as follows: • *Every 3 to 6 months, years 1 to 3.* This interval varies for patients receivir adjuvant chemotherapy, who need more frequent assessment during acti treatment. • *Every 6 months, years 4 and 5.* Some investigators prefer to continue ser examinations through year 8 because the rate of local recurrence is cons through that time interval. • *Annually after year 5.* More frequent follow-up may be needed for patient exceptionally high risk. <u>Schedule of imaging of the treated breast (**DCIS**)</u> A baseline mammogram during the first year after breast-conservation treatme least annually thereafter or at more frequent intervals as warranted by clinical radiographic findings. <u>Schedule of Imaging of the Treated Breast (**Stage I and II**)</u> A baseline mammogram performed for comparison 3 to 9 months after tumor and completion of all therapies; thereafter, at least annually or at more frequer intervals as warranted by clinical or radiographic findings. <u>Schedule of imaging of the contralateral breast (**DCIS and Stage I and II**)</u> The contralateral breast should undergo mammography annually, according to guidelines endorsed by both the American College of Radiology and the Amer Cancer Society. More frequent intervals may be warranted by clinical or radiog findings. *Evaluation of Sequelae* At the time of the first follow-up examination, and serially thereafter, the physic should evaluate the patient for any treatment-related toxicities, including: • Assessment of the overall cosmetic result. • Assessment of complications. Complications should be specified with reg

	symptomatology and physical findings. The use of the RTOG/EORTC (Ra Therapy Oncology Group/European Organization for Research and Treat Cancer) Radiation Toxicity Scoring Scheme is recommended for the grad Simple measurement of arm circumference at fixed distances above and the olecranon is recommended for the evaluation and quantification of arı edema. • The patient's evaluation of treatment outcomes in terms of psychological, functional, and cosmetic consequences. **Follow-up recommendations specific to Stage I and II:** Ultrasonography can characterize a postoperative mass, such as a seroma, as filled rather than solid. As these masses resolve and scars form, a spiculated s tissue density that mimics tumor may be seen on the mammogram. Additional radiographic projections of the site of tumor removal facilitate more confident radiographic interpretations. Symptomatic patients are justifiably evaluated wit medical tests (e.g., radionuclide bone scan, chest radiography, computerized tomography scans, liver function tests) as indicated by the character of their m problem. An annual chest radiograph may be appropriate in patients who smo
CCOPGI (1996-2000)	No recommendations offered.

TABLE 3: BENEFITS AND HARMS	
	Potential Benefits Associated with the Treatment of Early Breast Cancer
ICSI (2000)	Breast conservation therapy is an appropriate method of primary therapy for the r of women with Stage I or II breast cancer and is preferable because it provides su equivalent to total mastectomy and axillary dissection while preserving the breast Literature indicates a role for postoperative XRT in improving locoregional con survival for certain early stage patients with high risk features. These high risk include positive axillary lymph nodes (especially when four or more positive lyı nodes are present) pectoralis fascia involvement, primary tumor size greater th equal to five cm in maximal diameter, estrogen receptor negativity (when pres conjunction with other high risk features), and positive surgical margins.
SIGN (1998)	*General benefits* • Optimal management of breast cancer can increase the overall and disea survival rate and reduce the risk of disease recurrence • Improved quality of life. *Benefits of adjuvant systemic treatment* • The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) confirn adjuvant systemic treatment using cytotoxic agents and/or endocrine ther improves relapse free survival and overall survival in all age groups.

	Benefits of endocrine therapy • In the EBCTCG overview (1992) tamoxifen reduced the annual odds of recurrence by 25% and odds of death by 17%. This equates to a 6% impr in absolute survival at 10 years, but is greater in women with node positiv disease. These benefits apply to women of all ages but are largely confin women with ER positive (or ER unknown) tumors. *Benefits of chemotherapy* • In the EBCTCG overview combination chemotherapy reduced annual odc recurrence and death rates by 28% and 17% respectively. This equates t improvement in absolute survival at 10 years. The absolute benefits were for women with node positive disease, and although the effect was greate younger women, chemotherapy still significantly reduced recurrence in w aged 60-69.
ACR/ACS/CAP/SSO (1998)	*General benefits:* DCIS • Effective multidisciplinary diagnosis and management of ductal carcinom of the breast • Appropriate selection of patients for breast conservative surgery Stage I and II • Effective multidisciplinary diagnosis and management of invasive breast carcinoma • Appropriate selection of patients for breast conservative surgery *Benefits of specific treatment options for DCIS:* • Mastectomy: relapse rates of 1-2% have been reported for patients with b clinically evident and mammographically detected DCIS. Although maste results in cure rates approaching 100%, it may be overtreatment for patie DCIS, particularly those with small, mammographically detected lesions. • Breast-conserving surgery and radiation therapy: in a prospective randon study the breast cancer recurrence rate at eight years was 12.1%. The cr incidence of breast tumor recurrence reported in retrospective series rang 4% to 18%. Deaths caused by breast cancer have been reported in up to patients treated in studies with a median follow-up of 10 years or fewer. • Breast-conserving surgery alone: in a prospective randomized study the l cancer recurrence rate at eight years was 26.8%, significantly higher thar observed for breast-conserving surgery with radiation therapy. *Benefits of breast-conservation surgery compared to mastectomy in patients v Stage I or II breast cancer:* The results of prospective randomized trials and the results of large retrospect nonrandomized studies from single institutions have shown that breast-conser

	treatment and mastectomy are equally effective for appropriately selected pati early-stage breast cancer. Both treatment options are associated with overall s rates of 60-80% and disease-free survival rates of 50-70%, reported at 6-18 ye follow-up. Local recurrence rates following either treatment regimen range fron
CCOPGI (1996-2000)	DCIS • There is weak evidence from non-randomized controlled studies of DCIS subgroup analysis from an RCT demonstrating similar rates of local relap overall survival for mastectomy and lumpectomy with radiation. • Eight-year results from a randomized controlled trial in patients with DCIS detected a reduction in invasive local recurrence from 13.4% to 3.9% (p< and in non-invasive local recurrence from 13.4% to 8.2% (p=0.007) with a radiotherapy post lumpectomy. The overall mastectomy rate was also rec Survival rates were not significantly different between groups. • Current data suggest that size, margin status, grade and comedo type ne are predictors of local recurrence. In two large randomized trials, the EORTC 10853 and the National Surgic Adjuvant Breast Project (NSABP) B-17, ipsilateral breast irradiation follow breast conserving surgery has shown significant efficacy in reducing the r invasive and non-invasive breast recurrence in the ipsilateral breast. In th contralateral breast, the EORTC 10853 reported a significant association radiotherapy and an increased risk of developing contralateral breast can while the B-17 with longer follow-up, reported no significant difference. • There is some evidence to suggest that patients with small, low-grade les clear margins greater than 10mm have a sufficiently low risk of recurrenc forgo breast irradiation. Eligible patients should be encouraged to particip ongoing clinical trials. • It would be premature to recommend the routine use of tamoxifen in patie DCIS based on the evidence available. Although a randomized trial repor lower rate of recurrence with tamoxifen, these patients already have a lov recurrence, and the benefits of tamoxifen as demonstrated by this trial we in absolute terms. Stages I and II • In six randomized controlled trials (RCTs), no statistically significant differ were detected in survival between mastectomy and conservative therapy (lumpectomy). In one RCT, a statistically significant difference was detect favor of the mastectomy arm. However, this was an early trial with substa methodologic weaknesses. • All of 4 randomized controlled trials reviewed showed a significant decrea local recurrence rates for patients receiving radiotherapy. Despite the effe local recurrence, no difference in survival was detected in any of the four Most of the patients with breast recurrence in these trials underwent mast Adjuvant therapy • Adjuvant systemic therapy reduces recurrence of disease (26% relative r in the annual odds of recurrence for both chemotherapy and tamoxifen co with control) and improves survival (relative reduction in the annual odds compared with control was 18% for chemotherapy and 17% for tamoxifen patients with node-negative breast cancer. The choice of therapy (chemo

	or tamoxifen) should be based on the patient's risk of recurrence and on f which predict responsiveness to therapy (age and receptor status).
	Potential Harms Associated with the Treatment of Early Breast Cancer
ICSI (2000)	None stated.
SIGN (1998)	Lymphedema of the arm may occur in women with breast cancer due to lymph no damage caused by surgery and/or radiotherapy, or because of obstruction caused local tumor. All patients undergoing surgery and/or radiotherapy treatment to the a should receive pre-treatment information on lymphedema. (recommendation grad All women undergoing surgery which results in breast asymmetry should be of full breast prosthesis and fitting service. This should be offered by or in associ with a breast care nurse. (Recommendation grade B) Women should be warned of the risks of reduction of arm mobility following su and/or radiotherapy. They require advice and help with an appropriate progran exercises. (Recommendation grade B) Women should be informed regarding the potential effect of cancer treatment menopausal status, and advised regarding non-oestrogen alternatives and sel strategies which might alleviate their symptoms. (Recommendation grade B) A number of studies have examined the incidence of psychological and psych morbidity in women with breast cancer. They have shown a high risk of clinica significant levels of anxiety and/or depression, severe sexual difficulties and of problems related to body image. This is in addition to the normal reactions of v the diagnosis of a potentially life threatening illness and the side effects of trea All professionals involved in the management of patients with breast cancer sh have a high index of suspicion regarding the presence of psychological and ps problems. (Recommendation grade B)
ACR/ACS/CAP/SSO (1998)	Risks associated with exposure to irradiation.
CCOPGI (1996-2000)	DCIS • There is limited data related specifically to DCIS, but acute and chronic to likely to be similar to that associated with surgery and radiation treatment invasive disease. Stages I and II • An important concern regarding scheduling is the risk of increased acute complications from radiotherapy when it is given concurrently with chemo especially if anthracycline-based regimens are used.

	Adjuvant therapy • Adjuvant chemotherapy can be associated with adverse effects. The type adverse effect and its frequency is dependent on the chemotherapy regin Nausea and vomiting are generally well controlled with antiemetics. Alope (reversible) occurs in approximately 40% of patients receiving CMF-type chemotherapy. Hospitalization for febrile neutropenia occurs in approxima of patients. Amenorrhea occurs in approximately 50% of patients and ver thromboembolism in approximately 2% of patients. Anthracycline-contain chemotherapy is associated with more acute nausea and vomiting than C with complete alopecia. There is the theoretical risk of cardiac injury with anthracycline-based chemotherapy but it is likely to be very rare with con doses. Chemotherapy can theoretically be leukemogenic. Tamoxifen is associated with relatively few adverse effects. Up to 50% of women on ta experience hot flashes. Very rarely, tamoxifen can cause depression and thromboembolism. Recent studies have reported an approximate risk of endometrial cancer of one in 500.

TABLE 4: LEVELS OF EVIDENCE AND GRADES OF RECOMMENDATIONS

ICSI (2000)	I. **CLASSES OF RESEARCH REPORTS** A. **Primary Reports of New Data Collection:** Class A: Randomized, controlled trial Class B: Cohort study Class C: Non-randomized trial with concurrent or historical contro Case-control study; Study of sensitivity and specificity of a diagno Population-based descriptive study Class D: Cross-sectional study; Case series; Case report B. **Reports that Synthesize or Reflect upon Collections of Prima Reports:** Class M: Meta-analysis; Decision analysis; Cost-benefit analysis; effectiveness study Class R: Review article; Consensus statement; Consensus repor Class X: Medical opinion II. **CONCLUSION GRADES** Key conclusions (as determined by the work group) are supported by a c grading worksheet that summarizes the important studies pertaining to th conclusion. Individual studies are classed according to the system define Section I, above, and are assigned a designator of + (report has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data c and analysis), - (these issues have not been adequately addressed), or (t is neither exceptionally strong or exceptionally weak) to reflect the study d Conclusion grades are determined by the work group based on the follow definitions: **Grade I:** The evidence consists of results from studies of strong design fo answering the question addressed. The results are both clinically importa consistent with minor exceptions at most. The results are free of serious d about generalizability, bias, and flaws in research design. Studies with ne results have sufficiently large samples to have adequate statistical power **Grade II:** The evidence consists of results from studies of strong design f answering the question addressed, but there is uncertainty attached to th

	conclusion because of inconsistencies among the results from different st because of doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of re from weaker designs for the question addressed, but the results have bee confirmed in separate studies and are consistent with minor exceptions a **Grade III:** The evidence consists of results from a limited number of studi weak design for answering the question addressed. Evidence from studie strong design is either unavailable because no studies of strong design h done or because the studies that have been done are inconclusive due to generalizability, bias, design flaws, or inadequate sample sizes. **Grade IV:** The support for the conclusion consists solely of the statement informed medical commentators based on their clinical experience, unsubstantiated by the results of any research studies.
SIGN (1998)	**Statements of evidence:** **Ia** Evidence obtained from meta-analysis of randomized controlled trials. **Ib** Evidence obtained from at least one randomized controlled trial. **IIa** Evidence obtained from at least one well-designed controlled study wi randomization. **IIb** Evidence obtained from at least one other type of well-designed quasi experimental study. **III** Evidence obtained from well-designed non-experimental descriptive st such as comparative studies, correlation studies and case studies. **IV** Evidence obtained from expert committee reports or opinions and/or cl experiences of respected authorities. **Grades of Recommendations:** A. Requires at least one randomized controlled trial as part of a body of liter overall good quality and consistency addressing the specific recommend (Evidence levels Ia, Ib) B. Requires the availability of well-conducted clinical studies but no randomi clinical trials on the topic of recommendation. (Evidence levels IIa, IIb, III) C. Requires evidence obtained from expert committee reports or opinions ar clinical experiences of respected authorities. Indicates an absence of dire applicable clinical studies of good quality. (Evidence level IV)

GUIDELINE CONTENT COMPARISON

Guidelines developed by the Institute for Clinical Systems Improvement (ICSI), the Scottish Intercollegiate Guidelines Network (SIGN), the American College of Radiology in collaboration with the American College of Surgeons, College of American Pathologists and Society for Surgical Oncology (ACR/ACS/CAP/SSO), and Cancer Care Ontario Practice Guidelines Initiative (CCOPGI) present recommendations for the treatment of early-stage breast cancer. These recommendations are based on evidence available at the time of each report. All guidelines offer literature citations to support their major

recommendations. The guidelines from ICSI and SIGN rank the level of evidence for each major recommendation, following explicit schemes (see Table 4 above).

The scope of the guidelines varies. ICSI, for example, focuses on early stage breast cancer treatment, including treatment of ductal carcinoma in situ (DCIS), while SIGN covers screening, diagnosis, and treatment of breast cancer at all stages. SIGN also discusses rehabilitation, psychosocial aspects of breast cancer, and the role of the breast cancer nurse in treatment. Only select SIGN recommendations (as described in the Introduction) are included in this synthesis. ICSI and SIGN both discuss breast conservation therapy (surgery, radiation, adjuvant therapy) as well as mastectomy (including post-mastectomy radiation therapy), breast reconstruction, and follow-up. The guidelines from ACR/ACS/CAP/SSO target the specific areas of breast conservation treatment in early stage invasive breast cancer and DCIS. These jointly prepared guidelines focus on lumpectomy with axillary dissection and postoperative breast irradiation, including follow-up. ACR/ACS/CAP/SSO does not address mastectomy (in detail), post-mastectomy radiation therapy, or adjuvant systemic therapy (chemotherapy and endocrine therapy). The four CCOPGI guidelines pertain to very specific topics of breast cancer treatment, representing breast conservation surgery in DCIS and early stage invasive breast treatment, postoperative radiation, and adjuvant systemic therapy. CCOPGI also does not address mastectomy (in detail) or postmastectomy radiation therapy in these guidelines but is developing a separate guideline on local regional radiation therapy following mastectomy. The CCOPGI guideline on adjuvant systemic therapy is applicable to some women with more advanced breast cancer (Stages III-IV). The ICSI, SIGN, and CCOPGI guidelines make recommendations for adjuvant systemic therapy. Recommendations pertaining to neoadjuvant therapy are made by ICSI and SIGN only.

Areas of Agreement

Treatment Options and Discussion with Patient. Although the guidelines differ in how much emphasis they place on mastectomy for early stage breast cancer, all guidelines agree that eligible women should be given a choice between mastectomy with reconstruction and breast conservation surgery. They also agree that these options should be fully discussed with the patient and that patients should be educated about benefits and risks of each option.

Patient Eligibility for Conservation Surgery. There is general agreement that breast conservation surgery is absolutely contraindicated when patients are unable to complete radiation therapy. The presence of diffuse microcalcifications or gross multicentric or multifocal disease is also considered by all guidelines to be an absolute contraindication. Both ICSI and ACR/ACS/CAP/SSO agree that significant prior irradiation is an absolute contraindication to further radiotherapy. All of the guidelines acknowledge that the outcome of breast conservation surgery in the case of a large tumor and/or a small breast may be less than optimal.

Localization and Assessment of Breast Abnormalities. The guidelines are in general agreement on types of imaging and biopsy methods to be used for identification and localization of breast abnormalities. For palpable masses, these methods include fine needle aspiration, core-needle, and surgical biopsies. Nonpalpable lesions, including nonpalpable DCIS, require

preoperative radiographic localization; guide wires or bracketing wires are recommended for marking the lesions. Recent bilateral mammograms are standard in all cases.

Excisional Biopsy and Conservation Surgery (Lumpectomy). All of the guidelines agree that the goals of conservation surgery should be complete excision of the tumor with minimal cosmetic deformity. All guidelines acknowledge the need for removal of a small rim of normal breast tissue surrounding the lesion to reduce the risk of local recurrence. ICSI, ACR/ACS/CAP/SSO, and CCOPGI emphasize that the specimen should be given intact (not sectioned) to the pathologist, and that specimens should be carefully marked and oriented. Both ACR/ACS/CAP/SSO and CCOPGI recommend against frozen sections preparations of tissue obtained from nonpalpable lesions or microcalcifications, since freezing of tissue might interfere with pathological diagnosis. The need for specimen radiographs is generally acknowledged by all the guidelines.

Pathologic Evaluation of Breast Tissue. Although the guidelines differ in the amount of detail they give regarding the pathology report, all agree that the following should be included: assessment of tumor margins, grade of tumor, and estrogen receptor status. ICSI, SIGN, and ACR/ACS/CAP/SSO all acknowledge the need for the assessment of the amount of lymphatic invasion and the measured size of the tumor.

Mastectomy. All of the guidelines agree that mastectomy with the option of reconstruction is indicated for women ineligible for breast conservation surgery and for women who decline conservation surgery for personal reasons.

Axillary Surgery. All of the guidelines agree that axillary node sampling (as a minimum) or clearance is required in all patients with operable invasive breast cancer. The procedure is necessary for both staging purposes and to reduce the risk of regional axillary recurrence. Removal of level I and level II lymph nodes is recommended by all of the guidelines; level III dissection is recommended only when obviously necessary because of invasive disease. The guidelines are in general agreement that axillary dissection is not necessary in patients with noninvasive DCIS, since axillary node metastases are rare. ICSI, ACR/ACS/CAP/SSO, and CCOPGI all recommend that axillary incisions be undertaken through an incision separate from the breast incision. ICSI, SIGN, and ACR/ACS/CAP/SSO note that sentinel node biopsy cannot be recommended as a standard practice, since this procedure is still investigational.

Radiation Therapy. All of the guidelines agree that radiation therapy is essential after breast conservation therapy. The ACR/ACS/CAP/SSO and ICSI guidelines are in agreement that irradiation of the whole breast following breast conservation surgery should be 4500-5000 cGy (180-200 cGy per fraction). The CCOPGI guideline notes that the optimal fractionation schedule for breast irradiation has not been established and the role of boost irradiation is unclear. The CCOPGI guideline does, however, make the following suggestion: “Outside of a clinical trial, two commonly used schedules are suggested: 50 Gy in 25 fractions to the whole breast, or 40 Gy in 16 fractions to the whole breast with a local boost to the primary site of 12.5 Gy in five fractions.” The SIGN guideline does not offer details on fractionation schedules. ICSI, SIGN, and ACR/ACS/CAP/SSO agree that axillary irradiation

is usually unnecessary following a complete axillary dissection; however, both ICSI and ACR/ACS/CAP/SSO state, that radiation might be considered, in the case of a large number (4 or more) of positive axillary lymph nodes.

Adjuvant Systemic Therapy. ICSI, SIGN, and CCOPGI agree that adjuvant therapy (chemotherapy and endocrine therapy) should be considered in women with invasive (Stage I-II) breast cancer. Both ICSI and SIGN recommend that women be enrolled in clinical trials whenever possible. All of the recommended chemotherapy protocols encompass cyclophosphamide, methotrexate, and 5-fluorouracil, and doxorubicin. The decision to implement therapy and the particular choice of therapy depends on the patient's age (or menopausal status), the risk for recurrence, and the ER status of the tumor. (ICSI also considers PR status in its recommendations). All of the guidelines, including ACR/ACS/CAP/SSO, agree that tamoxifen is not indicated for treatment of DCIS. In general, tamoxifen is recommended only in women with ER positive tumors (or ER status unknown), although ICSI also recommends tamoxifen for PR positive tumors.

Neoadjuvant Therapy. ICSI and SIGN are the only guidelines offering recommendations on neoadjuvant therapy, and both agree that its use may make breast conservation possible in selected patients who might otherwise have to undergo mastectomy. Both guidelines advise that this therapy be administered under the auspices of a clinical trial.

Follow-up Care. ICSI, SIGN, and ACR/ACS/CAP/SSO all give recommendations on follow-up care, but in varying degrees of detail. In general, the follow-up includes clinical examination and mammography of the treated and contralateral breast, although there is some difference among guidelines on the scheduling of mammograms (see below under Areas of Difference).

Areas of Differences

Patient Eligibility for Conservation Surgery. The guidelines differ in some of their designations of absolute and relative contraindications for breast conservation therapy and radiation therapy. ACR/ACS/CAP/SSO, for example, considers collagen vascular disease (e.g., lupus erythematosus, scleroderma) to be an absolute contraindication to radiation therapy, whereas ICSI considers this condition to be a relative contraindication. ACR/ACS/CAP/SSO lists pregnancy as an absolute contraindication for radiation therapy, although it adds that conservation surgery can sometimes be performed in the third trimester, with radiation therapy administered after delivery. CCOPGI considers both scleroderma and pregnancy to be contraindications. The SIGN guideline considers age to be a potential factor in the eligibility for breast conservation therapy noting that patients aged less than 35 years are at increased risk of local recurrence, while the ICSI and ACR/ACS/CAP/SSO guidelines explicitly state age is not a consideration. The CCOPGI guideline suggests eligible elderly women or those with comorbid medical conditions may be better served with mastectomy and the ACR/ACS/CAP/SSO notes that in the elderly, physiologic age and the presence of comorbid conditions should be the primary determinants of local therapy. Tumor size per se is not considered a contraindication for breast conservation therapy in the ACR/ACS/CAP/SSO guideline (acknowledging there are few data on treatment of tumors >5cm), while the ICSI guideline rules out breast conservation when tumor size is >5cm.

Localization and Assessment of Breast Abnormalities. For symptomatic patients, SIGN recommends avoiding mammograms in patients under 35 years of age, while other guidelines do not mention age restrictions in this context.

Radiation Therapy. Boost irradiation is considered standard of care in the ICSI guideline, while in the ACR/ACS/CAP/SSO and CCOPGI guidelines boost radiation is considered controversial, though often done.

Adjuvant Therapy. SIGN is the only guideline that specifically recommends tamoxifen for low-risk, pre- or perimenopausal women with ER positive disease. CCOPGI states that pre- and postmenopausal women at low or minimal risk should not receive adjuvant therapy. SIGN is also the only guideline to consider and recommend ovarian ablation in pre-menopausal women with ER positive tumors. SIGN's grade A recommendation is based on an Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview *[Early Breast Cancer Trialists' Collaborative Group. Ovarian ablation in early breast cancer: overview of the randomized trials. Lancet 1996; 348:1189-1198.]* and a Scottish clinical trial *[Scottish Cancer Trials Breast Group and ICRF Breast Unit, Guy's Hospital, London. Adjuvant ovarian ablation versus CMF chemotherapy in premenopausal women with pathological stage II breast carcinoma: the Scottish trial. Lancet 1993; 341:1293-1298]*. This particular evidence was not referenced in the other guidelines offering adjuvant therapy recommendations. ICSI is the only guideline that specifically states that chemotherapy may be advised for women up to age 70 years if the patient's anticipated life expectancy is more than 10 years.

Follow-up care. Baseline mammography after breast conservation surgery is recommended to be obtained at 3-9 months after excision in the ACR/ACS/CAP/SSO guideline, and at 1 year in the SIGN guideline. Subsequent mammography is to be obtained at least annually in the ACR/ACS/CAP/SSO guideline, annually in the ICSI guideline, and every 1-2 years in the SIGN guideline.

Updates in Progress: Updates in Progress: The Institute for Clinical Systems Improvement (ICSI) is currently updating their guideline. The Scottish Intercollegiate Guidelines Network (SIGN) guideline is being reviewed in 2001-2002. Cancer Care Ontario Practice Guideline Initiative (CCOPGI) is currently updating the "Surgical Management of Early Stage Invasive Breast Cancer (Stage I and II)" and "Breast Irradiation in Women with Early Stage Invasive Breast Cancer Following Breast Conservation Surgery" guidelines. Regarding the adjuvant systemic therapy guideline, CCOPGI notes that although there is new evidence, they will review and endorse an updated guideline related to this topic developed by another group.

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